Role and potentials of low-flow CO2 removal system in mechanical ventilation.

Role and potentials of low flow CO_2 removal system in mechanical ventilation

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ABSTRACT

Purpose of review: An analysis of the technological implementation of extracorporeal CO_2 removal ($ECCO_2R$) techniques, and of its clinical application. A new classification of $ECCO_2R$ based on technological aspects, clinical properties and physiological performances, is proposed.

Recent findings: The use of a ventilation with lower tidal volumes have been proved successful in Acute Respiratory Distress Syndrome (ARDS) patients but can be extremely problematic, especially when dealing with respiratory acidosis. The implementation of extracorporeal CO_2 removal devices can represent the missing link between prevention of ventilator induced lung injury and pH control. $ECCO_2$-R has attracted increasing interest because new less invasive approaches allowing an easier management of ARDS patients. Recent studies have also shown that $ECCO_2$-R can also be used in patients with exacerbation of Chronic Obstructive Pulmonary Disease (COPD) and as bridge to lung transplantation.

Summary: *The future ventilatory management of patients with acute respiratory failure may include a minimally invasive extracorporeal carbon dioxide removal circuit associated with the least amount of ventilatory support (non-invasive in COPD and/or invasive in ARDS) to minimize sedation, prevent ventilator-induced acute lung injury, and nosocomial infections. Randomized clinical trials in the pipeline will confirm this fascinating hypothesis.*

Key words: Extra-Corporeal CO_2Removal ($ECCO_2R$); ECMO; protective ventilation; lung support; ventilator induced lung injury (VILI).

Mechanical ventilation (MV) is the main form of life support for patients with acute respiratory failure, and can resolve the impairment of gas exchange alteration in the vast majority patients with acute respiratory failure.[1] However, evidences have progressively emerged suggesting that MV, although indispensable for survival, may worsen the injured lung and may increase mortality rate if inappropriately administered.[2, 3] This is particularly true for acute respiratory distress syndrome (ARDS), where several studies demonstrated that the main reason for high mortality (30-50%) is not the severe hypoxemia but rather multi-organ failure (kidneys, heart, liver, etc.), potentially caused by the translocation of various mediators from the lungs through the systemic circulation to peripheral organs caused and/or augmented by artificial ventilation (ventilator-induced lung injury, VILI).

The randomized trial carried out by the National Institute of Health demonstrated that ventilating patients with a tidal volume (V_T) of 6 ml/kg (calculated from predicted body weight, PBW), and with a maximum end-inspiratory plateau pressure (P_{PLAT}) of 30 cmH_2O instead of ventilating patients with a V_T of 12 ml/kg PBW decreased mortality from

39.8% to 31%. [4] However, observational studies carried out in Europe and in the US demonstrated that there was poor compliance by clinicians in reducing ventilation volumes and pressures in order to minimize iatrogenic damage caused by mechanical ventilation. A major reason for the underuse of protective ventilatory strategies is the hypercapnia caused by the reduction in ventilatory volumes. Furthermore, recent studies have shown that lung hyperinflation still occurs in approximately 30% of ARDS patients even though they are being ventilated "correctly" using the ARDSNet strategy [5]. These studies also suggested that some patients may benefit from a further reduction of V_T even when P_{PLAT} is less than 30 cmH_2O. [5, 6] Bellani and coworkers recently assessed the intensity of pulmonary inflammation during mechanical ventilation using positron-emission tomography (PET) imaging of (18F) fluoro-2-deoxy-D-glucose to detect the presence of metabolically active inflammatory cells. [7] They showed that P_{PLAT} is significantly correlated with metabolic activity, and the correlation increases steeply above 26-27 cmH_2O thus suggesting that further limitation of ventilation to values of P_{PLAT} of 25 cmH_2O or lower may be associated with lower degree of pulmonary inflammation due to less VILI. [7] (**).

The idea of partial support (removing only carbon dioxide, with little to no impact on oxygenation: partial extracorporeal support) was proposed in 1977 by Kolobow [8, 9] and Gattinoni.[10] These authors suggested that applying only a few ventilator breaths at low volumes and low peak inspiratory pressures ("lung rest") could prevent damage to the compromised lungs. To reduce complexity, expenses, and side effects of extracorporeal lung assistance, Pesenti and coworkers modified an extracorporeal circuit designed for renal replacement therapy by adding to the circuit an oxygenator and proposed the concept of removing "*only a portion of* carbon dioxide *production*" to allow less traumatic ventilator settings.[11] This hypothesis was developed taking into consideration the original observation of Sherlock and coworkers who found that patients treated with haemodialysis experienced a transient hypocapnia, hypoventilation and hypoxemia due to the capacity of the hemofilter to remove a significant amount of CO_2.[12] What Kolobow, Gattinoni and Pesenti therefore proposed may be interpreted nowadays as the optimal protective ventilatory strategy that, "disconnecting" oxygenation (provided using the "residual" functional lungs using PEEP and high

FiO2) from CO_2 clearance (performed used extracorporeal circuit and membrane lungs), may minimize/prevent VILI.

CARBON DIOXIDE REMOVAL: PHISIOLOGY AND TECHNIQUES

The use of extracorporeal circuits to support respiratory functions may be described using a *"continuous model"* that analyze and integrates the technological aspects (type of pump, characteristics of the oxygenator, type and size of catheter), the clinical properties (kind of surgical approach) and the physiological performances (amount of oxygen transferred to the patient and of carbon dioxide removed from the patient).[13] (**Table 1**).

The lowest complexity level is represented by **renal support** that requires very low blood flows, is less invasive for the patients requiring low primer volumes and a small coaxial catheter. With this technique carbon dioxide is extracted although a very low levels.[12, 14]

At the other extreme of the complexity scale, **total extracorporeal support (ECMO)** is able to completely supply the physiological blood gas exchanges, normally performed by the native lungs and is therefore capable of delivering oxygen and of removing CO_2 equal to the entire metabolic needs of the patient. It is an invasive and complex system, which needs high blood flows (equivalent to the entire cardiac output) and high diameter cannulation. It is also necessary to use high heparin dosage and elevated volume of priming. This device can be connected to patient with a venous-arterial (V-A) setting, therefore in parallel with the pulmonary circulation, also able to support the cardiac function, or in a venous-venous (V-V) setting, sequentially to the pulmonary circulation, preferred in case on respiratory failure alone.

Partial extracorporeal support ($ECCO_2$-R) represents the intermediate level of technical complexity. V-V $ECCO_2R$ needs a 14Fr coaxial catheter, to allow a blood flow of 0.3-0.5 l/min that is constantly guarantee by a roller non-occlusive pump designed to minimize hemolysis; blood is driven through an oxygenator membrane, which is connected to an oxygen source of 6-8 l/min. Some devices also include an hemofilter is series with the oxygenator to allow the extraction of

plasmatic water that is then reinfused in the circuit in order to lower hematocrit and prevent blood clotting.[15, 16] (**)

A centrifugal pump, that creates a radial flow going through an annular fiber oxygenator, has also been used in other veno-venous $ECCO_2R$ systems. This design maximizes the exchange surface, and therefore the device efficiency.[15] Both technological implementations are able to remove up to 25% of carbon dioxide production, and can transfer no more than 10 ml/min of oxygen. Low dose of heparin (4-18 IU/min) are necessary to avoid clotting occurrence.[15-17]

CLINICAL USE OF $ECCO_2R$

A brief overview of past years studies exploring $ECCO_2R$ techniques safety and feasibility is shown in Table 2.

ARDS

Gattinoni and coworkers reported the first systematically collected clinical experience of the use of $ECCO_2R$ in patients with severe ARDS. MV was limited to apneic oxygenation and to 3-5 sighs every minute with a peak inspiratory pressure < 35-45 cmH_2O; PEEP ranged between

15 and 25 cmH_2O. Carbon dioxide removal was performed using a pump-driven veno-venous bypass allowing blood flow to pass through two membrane lungs (9 m^2 total membrane surface area). Extracorporeal blood flow was progressively increased from 200 to 300 mL/min to the selected maintenance flow (20-30 % of cardiac output). Although the observed mortality rate was lower than expected, there was no concurrent randomized control group; as well, several episodes of severe bleeding were reported.[18] In 1993 Brunet and coworkers achieved a mortality rate of 50% in ARDS patients, utilizing a V-V $ECCO_2R$ coupled with protective ventilation that reached a maximum tidal volume of 325ml. They also reported a 21% of hemorrhagic events and an 8% of peripheral vascular problems.[19] One year later, Morris and coworkers presented results of a randomized controlled trial in ARDS patients that investigated the use of Pressure Controlled Inverse-Ratio Ventilation *vs* $ECCO_2R$ techniques associated to MV. The trial, showing no significant difference in survival (38%) between the two groups, also highlighted numerous episodes of severe bleeding and the need of major anticoagulation with consequent hemorrhagic complications.[20]

In 2006 Bein and coworkers published a retrospectively experience with an artero-venous pumpless device with an interposed membrane oxygenator sustained by patients hemodynamic. This artificial lung was able to remove up to 50% of the total body CO_2 production, with a blood flow of around 1-2 l/min. Authors reported occurrence of serious complications in 24,4% of patients with also episodes of ischemia of lower limbs after arterial cannulation.[21]

Under these circumstances, the clinical and technological implementation of $ECCO_2$-R implemented until few years ago is closer to full extracorporeal support, than to what envisioned in the "simple" devices as described in Table 1. The more invasive and/or complex systems are characterized by: *a) flow equal or higher than 1000 ml*; *b) wide bore catheters*; *c) high doses of heparin*; *d) large volumes of blood to "prime" the circuit*; *e) numerous blood transfusion due to loss in the circuitry and from the accesses.* The rates of major complications reported in clinical studies using $ECCO_2$-R are reported in TABLE 2B. These data help explain why $ECCO_2$-R has been limited to the sickest patients in whom all other treatments have failed [22] and to centers with large expertise.[23, 24]

In 2009 Terragni and coworkers presented a ventilation model of very low V_T (4ml/kg of predicted body weight) for severe ARDS patients that, despite a ventilation setting derived from the ARDS*net* Trial [4], showed morphological evidence of tidal hyperinflation.[5] This ventilatory model, that was proven to be able to decrease inflammatory markers associated with VILI, was coupled with a V-V $ECCO_2R$ device, which allowed to a safely and efficiently manage of acidosis resulted from V_t reduction. [16]

The device used in Terragni's study represents a modification of renal replacement therapy circuits, and is characterized by: *a) veno-venous by-pass systems; b) extracorporeal blood flow of 0.3-0.5 litres/min*; *c) smaller bore catheters or a single co-axial catheter similar to those currently used for renal ultrafiltration procedures*; *d) very low doses or no heparin; e) minimal volumes for "priming"*. This technological implementation of LFPPV–$ECCO_2$-R is therefore closer to device for renal replacement therapy than full ECMO (TABLE 1) and may explain the lack of significant side effects during the use of low-flow CO2 removal by-pass (TABLE 2B).

Chronic Obstructive Pulmonary Disease (COPD)

$ECCO_2R$ techniques could also represent a revolutionary tool for the approach of other clinical situations like chronic obstructive pulmonary disease (COPD) exacerbations treatment in patients at risk of non-invasive ventilation failure, or the intracranial bleeding management when associated to severe ARDS. Garcia and coworkers recently presented preliminary data on the attempt to optimize ECMO in patients with COPD to reduce ventilatory support. The study reports 10 patients (mean age of 45±14 years,) treated with ECMO during weaning from all respiratory support or as bridge to lung transplant. The mean duration of extracorporeal membrane oxygenation was 20 (9–59) days, with average mean blood flows of 3.5 (1.6–4.9) L/min, and levels of CO2 removal and O2 transfer of 228 (54–570) mL/min and 127 (36–529) mL/min, respectively. Six of 10 patients were weaned from respiratory support or underwent transplantation and survived to discharge from the hospital. The remaining 4 patients died of sepsis and withdrawal of care.[25] (**)

Bridge to lung transplant

$ECCO_2R$ devices with pump support, have been developed as bridges to lung transplant in patients with severe, unresponsive respiratory failure. In a recent report $ECCO_2$ R low flow devices have been proved simple and efficient methods to support patients with mild hypoxia and severe hypercapnia refractory to MV.[26](**) Ruberto et all reported also the experience of veno-venous extracorporeal support in primary graft dysfunction after single lung transplant with a control of respiratory acidosis, decrease of $PaCO_2$ and reduction of ventilatory support.[27](**)

CONCLUSIONS

Technological improvement has permitted the creation of new devices that are able to perform extracorporeal CO_2 removal at lower blood flows with less invasiveness. However our knowledge is limited to case reports and case series studies. Future randomized clinical trials that will soon be initiated various studies will help physicians to consider minimally invasive extracorporeal CO_2 removal devices, coupled with mechanical ventilation setting as an alternative to mechanical ventilation alone to prevent and/or minimize side effects of ventilatory support.

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Table 1:

Extracorporeal support techniques

Table 2:

Characteristics of the LFPPV–ECCO$_2$-R devices used in some of the largest studies from 1984 to 2009.